Disease Severity, Pregnancy Outcomes and Maternal Deaths among Pregnant Patients with SARS-CoV-2 Infection in Washington State

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Condensation

The COVID-19 hospitalization and case fatality rate in pregnant patients in a multi-center retrospective cohort study in Washington State was significantly higher than in similarly aged adults.

Short Title

COVID-19 Disease/Mortality in Pregnancy

AJOG At A Glance

A. Why was the study conducted? Whether COVID-19 poses a risk for pregnant women to develop severe or critical disease and the impact on maternal mortality and morbidity is poorly understood.
B. What are the key findings? In a multi-center retrospective cohort study of facilities covering 61% of annual births in Washington State, there were 240 pregnant patients with SARS-CoV-2 infections, 24 COVID-19-associated hospitalizations (10%) and 3 maternal deaths (1.25%). The COVID-19 case fatality rate in pregnant patients was 13.6-fold higher compared to similarly aged individuals with COVID-19
C. What does this study add to what is already known? Our data suggests the impact of COVID-19 on pregnant patients is greater than currently appreciated with an elevated risk for maternal death.

Keywords: COVID-19, SARS-CoV-2, coronavirus, pregnancy, pneumonia, maternal mortality, case-fatality, preterm birth, fetus

STRUCTURED ABSTRACT

Background: Evidence is accumulating that coronavirus disease 2019 (COVID-19) increases the risk for hospitalization and mechanical ventilation in pregnant patients and for preterm delivery. However, the impact on maternal mortality and whether morbidity is differentially affected by disease severity at delivery and trimester of infection is unknown.

Objectives: To describe disease severity and outcomes of SARS-CoV-2 infections in pregnancy across Washington State including pregnancy complications and outcomes, hospitalization, and case fatality.

Study Design: Pregnant patients with a polymerase chain reaction confirmed SARS-CoV-2 infection between March 1 and June 30, 2020 were identified in a multi-center retrospective cohort study from 35 sites in Washington State. Sites captured 61% of annual state deliveries. Case fatality rates in pregnancy were compared to COVID-19 fatality rates in similarly aged adults in Washington State using rate ratios and rate differences. Maternal and neonatal outcomes were compared by trimester of infection and disease severity at the time of delivery.

Results: The principal study findings were: 1) among 240 pregnant patients in Washington State with SARS-CoV-2 infections, 1 in 11 developed severe or critical disease, 1 in 10 were hospitalized for COVID-19, and 1 in 80 died; 2) the COVID-19-associated hospitalization rate was 3.5-fold higher than in similarly-aged adults in Washington State [10.0% vs. 2.8%; rate ratio (RR) 3.5, 95% confidence interval (CI) 2.3-5.3]; 3) pregnant patients hospitalized for a respiratory concern were more likely to have a comorbidity or underlying conditions including asthma, hypertension, type 2 diabetes, autoimmune disease, and Class III obesity; 4) three maternal deaths (1.3%) were attributed to COVID-19 for a maternal mortality rate of 1,250/100,000 pregnancies (95%CI 257-3,653); 5) the COVID-19 case fatality in pregnancy was a significant 13.6-fold (95%CI 2.7-43.6) higher in pregnant patients compared to similarly aged individuals in Washington State with an absolute difference in mortality rate of 1.2% (95%CI -0.3-2.6); and 6) preterm birth was significantly higher among women with severe/critical

COVID-19 at delivery than for women who had recovered from COVID-19 (45.4% severe/critical COVID-19 vs. 5.2% mild COVID-19, p<0.001).

Conclusions: COVID-19 hospitalization and case fatality rates in pregnant patients were significantly higher compared to similarly aged adults in Washington State. This data indicates that pregnant patients are at risk for severe or critical disease and mortality compared to non-pregnant adults, as well as preterm birth.

INTRODUCTION

In the early months of the coronavirus disease of 2019 (COVID-19) pandemic, pregnant patients faced uncertain risks associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.(1) SARS-CoV-2 infection in pregnancy is now known to result in a spectrum of asymptomatic to critical maternal disease.(2-7) Evidence is accumulating that pregnant patients with SARS-CoV-2 infections are at higher risk for hospitalization, mechanical ventilation, intensive care unit (ICU) admission and preterm birth.(2, 7-11) In June of 2020, a U.S. population-based study by the Centers for Disease Control (CDC) found that pregnant patients with SARS-CoV-2 infections were at higher risk for hospitalization, mechanical ventilation and ICU admission, but mortality rates were similar between pregnant and non-pregnant reproductive age women (0.2%).(8) A subsequent CDC study including more cases and restricted to symptomatic cases in pregnancy found an increased risk of mortality among pregnant women versus non-pregnant women with SARS-CoV-2(12), leading the CDC to revise public health guidance to indicate that pregnant women are at risk for severe COVID-19 disease.(9) However, as pregnancy status was missing or unknown in up to three-quarters of COVID-19 cases reported to the U.S. CDC, these results may be biased and the extent to which pregnant women experience severe or critical disease with increased risk for mortality needs further evaluation.(8, 10)

Additional population-based studies of COVID-19 in pregnancy including fatality rates in pregnancy would help determine the extent to which pregnant patients with COVID-19 are at risk for severe or critical disease similar to the 2009 H1N1 influenza pandemic.(13-15) Inclusion of all pregnant patients with SARS-CoV-2 including milder and asymptomatic cases managed as outpatients is critical for determining the impact of COVID-19 on pregnancy outcomes and the possibility of severe/critical maternal disease. Further, whether the timing of SARS-CoV-2 infection (e.g. trimester of infection, status at time of delivery) is associated with adverse pregnancy outcomes, such as hypertensive disease in pregnancy and/or preterm birth has not been thoroughly interrogated. We established the Washington State COVID-19 in Pregnancy Collaborative (WA-CPC) as a multi-center retrospective cohort study to capture COVID-

19 cases in pregnancy.(2) The WA-CPC network captures the majority of annual deliveries in the state, gathers clinical data on COVID-19 outcomes in pregnancy and shares information and strategies to improve patient care. The objective of this study was to describe disease severity and outcomes of COVID-19 in pregnancy across Washington State including pregnancy complications and outcomes, hospitalization, and case fatality.

METHODS

Washington State COVID-19 in Pregnancy Collaborative

The WA-CPC includes 35 large hospitals (n=22) and clinic systems providing prenatal care (n=13) in Washington State, encompassing 61% of the approximate 86,000 annual state deliveries (Table S1).(16) The majority of the participating hospitals had instituted universal screening for SARS-CoV-2 by nasopharyngeal swab prior to or at the time of the delivery admission by May 2020 (March=14%, April=64%, May=76%), with the remaining hospitals initiating universal testing for scheduled delivery admissions only.

Eligible cases were pregnant patients (≥18 years old) with a polymerase chain reaction (PCR) test confirmed SARS-CoV-2 infection during any trimester of pregnancy detected between March 1-June 30, 2020.(16) Pregnant women were tested for many reasons including exposure to a known SARS-CoV-2 case, symptoms, recent travel, personal requests and universal screening at labor and delivery. Collaborating sites identified eligible patients using diagnostic codes and site-specific algorithms. De-identified data were abstracted from electronic medical records and each record was reviewed by a second abstractor for quality control.(2) Final disease and delivery outcome data were abstracted between July 7-September 10, 2020 based on site capacity. COVID-19 disease severity was defined as: (1) mild (asymptomatic, non-pneumonia, mild pneumonia); (2) severe (dyspnea, respiratory rate of ≥30 breaths/min, percutaneous oxygen saturation of ≥93% on room air at rest, arterial oxygen tension over inspiratory oxygen fraction of<300mmHg, or lung infiltrates >50% within 24 to 48 hours; and (3)

critical (severe respiratory distress, respiratory failure requiring mechanical ventilation, shock, or multiple organ dysfunction or failure).(17, 18) Hospitalized participants were considered “hospitalized due to COVID-19 concern” based on the reason for admission noted by the abstracting team, including respiratory concerns and “other” COVID-19 concerns. Patients admitted for concurrent obstetrical (ex: delivery) and COVID-19 concerns were considered hospitalized for COVID-19 concern.

This multi-site medical records review was approved by Institutional Review Boards (IRB) at the University of Washington (STUDY# 00009701, approved 03/06/2020) and Swedish Medical Center (STUDY #2020000172, approved 03/19/2020). All other sites entered into reliance agreements with the University of Washington IRB.

Statistical Analyses

Demographic and SARS-CoV-2 infection characteristics in pregnancy were summarized by proportions and medians (interquartile range, IQR) overall and were compared across COVID-19 hospitalization status using chi-squared and Kruskal-Wallis tests. Maternal, delivery, and neonatal outcome characteristics were summarized for patients who had delivered by the time of final chart abstraction. These characteristics were described overall, by trimester of infection, and by the patient’s COVID-19 status at the time of delivery. Pregnant patients were categorized as ‘COVID-19 recovered’ if they were SARS-CoV-2 negative at the time of delivery or their last positive test was >14 days prior to delivery in alignment with quarantine guidelines during the study period; this categorization was independent of disease severity. Women who were SARS-CoV-2 PCR positive in the preceding 14 days of delivery or admitted with post-COVID-19 complications at the time of delivery (even in absence of continued PCR positivity) were considered to have “active COVID-19” and further classified by mild or severe/critical disease status. Delivery outcomes were compared between COVID-19 recovered, mild COVID-19, and severe/critical COVID at delivery and by trimester of infection, using the chi-squared and Kruskal-Wallis tests, where appropriate.

Collaborating sites captured the majority of pregnancies in Washington State with the highest coverage in regions most affected by COVID-19 (Table S1).(19) We calculated crude rate ratios (RR) and rate differences (RD) with Poisson exact 95% CIs to compare COVID-19-associated hospitalization and case fatality rates in our study population to rates experienced by 20-39 year old adults with SARS-CoV-2 in Washington State using publicly available data from the Washington State Department of Health (WA DOH); this comparison group served as the best publicly available proxy for rates in reproductive aged women as data were only available by age group or gender, but not both.(19) Notably, non-pregnant adults were tested for SARS-CoV-2 for the same reasons as pregnant people including by universal screening prior to medical procedures. Hospitalization and case fatality rates at the state level were estimated between March 1, 2020-September 26, 2020 since outcomes were collected for some study participants through September, and to account for the lag between infection detection and mortality outcomes. Both crude RR and RD were calculated given the small number of events in this study population to ascertain both relative and absolute risk.

Results

SARS-CoV-2 Infections in Pregnancy

Two hundred and forty confirmed cases of SARS-CoV-2 infections in pregnancy were detected by WA-CPC sites including 24 (10.0%) who were hospitalized for a COVID-19 respiratory concern. Demographic and co-existing conditions are reported in Table 1. Of these, forty-six cases were previously published including details on 8 deliveries.(2) Median age was 28 years old (IQR 24-33.5). Nearly half were White (113/240) and half reported Hispanic ethnicity (126/240). Two-thirds were publicly insured (160/240). The most common underlying conditions were pre-pregnancy obesity (body mass index ≥30.0, 45.3% (102/225), asthma (8.3%, 20/240), type 2 diabetes (5.4%, 13/240), and hypertension (4.6%, 11/240). Pregnant patients with SARS-CoV-2 infections who were

hospitalized for a COVID-19 concern were slightly older (median 32 years old vs 28, p=0.04) and more likely than non-hospitalized pregnant patients with SARS-CoV-2 infection to have at least one comorbidity or underlying condition (45.8% vs 17.6%, p=0.001), such as asthma (20.8% vs 6.9%, p=0.02), hypertension (20.8% vs 2.8%, p<0.001), type 2 diabetes (12.5% vs 4.6%, p=0.11), autoimmune disease (8.3% vs 0.9%, p<0.01), and Class III obesity (21.1% vs 6.3%, p=0.01; Table 1).

Approximately half of the SARS-CoV-2 cases were detected in the third trimester (56.3%, 135/240), with 27.9% (67/240) in the second trimester, and 15.8% (38/240) in the first trimester (Table 2). At the time of the first positive COVID-19 test, 77.1% (185/240) of pregnant patients were symptomatic (or reported resolved COVID-19 symptoms) with the remaining being asymptomatic (22.9%, 55/240). Mild COVID-19 disease occurred in 90.8% (158/240, including 55 asymptomatic cases), with severe and critical disease occurring in 7.5% (18/240) and 1.7% (4/240), respectively. Three maternal deaths due to COVID-19 complications occurred (1.3%, 3/240).

Pregnant Patients Hospitalized for COVID-19-associated Respiratory Concern

Twenty-four cases (10.0%) were hospitalized specifically for COVID-19 symptoms, with three having concurrent delivery related indications (Table 3). One-third of the hospitalized patients (8/24) were admitted to the ICU (3.3% of study population, 8/240); one pregnant patient was hospitalized and admitted to the ICU twice. Overall, the SARS-CoV-2 hospitalization rate in pregnant patients was 3.5-fold higher than the rate among individuals aged 20-39 with confirmed SARS-CoV-2 in Washington State [10.0% (24/240) vs. 2.8% (985/34,902); RR 3.5, 95%CI 2.3-5.3] (Table 4).

Most pregnant patients hospitalized for COVID-19 had severe or critical disease (79.2%, 19/24), but 20.8% (5/24) admitted for a COVID-19 concern were ultimately considered to have mild disease by the disease severity criteria (Table 2).(17, 18) All four pregnant patients with critical COVID-19 disease developed confirmed or suspected acute respiratory distress syndrome; three of these patients ultimately died. Almost half (40.9%, 9/22) of the hospitalized patients delivered during their admission

for COVID-19 (Table 3). Nineteen of the hospitalized patients (79.1%, 19/24) received some level of oxygen support, with 16.7% (4/24) of hospitalized patients receiving mechanical ventilation. Laboratory testing in addition to a SARS-CoV-2 PCR was performed on a minority of patients, who typically had severe/critical COVID-19. Using pregnancy-specific norms for laboratory values (20), 43.5% (10/23) had lymphopenia, 77.3% (17/22) had an elevated aspartate aminotransferase, 53.3% (8/15) had an elevated C-reactive protein, 29.4% (5/17) had an elevated D-Dimer, and 4.4% (1/23) had an elevated creatinine during COVID-19 associated hospitalization (Table 3). The most common targeted treatments for COVID-19 disease among hospitalized pregnant patients were remdesivir (37.5%, 9/24), followed by dexamethasone (12.5%, 3/24), hydroxychloroquine (8.3%, 2/24), and convalescent plasma (8.3%, 2/24) with some patients receiving multiple therapies.

Maternal Deaths in Pregnant Patients with SARS-CoV-2 Infection

There were three deaths among 240 pregnant patients with a SARS-CoV-2 infection for a maternal mortality rate of 1,250/100,000 pregnancies (95%CI 258-3,653) (Table 4). Overall, the SARS-CoV-2 case fatality rate among included pregnant patients was a significant 13.6-fold higher in pregnant patients than the 91.7/100,000 rate in similarly aged 20-39 year olds in Washington State (RR 13.6, 95%CI 2.7-43.6); equating to an absolute rate difference of 1.2% (95%CI -0.26-2.57; Table 4). The three deaths in pregnant patients constitute 9.4% (3/32) of the total deaths in this age group in Washington State assuming all three deaths were included in the state's surveillance data.

The three pregnant patients who died due to COVID-19 disease were all publicly insured, 35-39 years old and from minority racial-ethnic groups. Each had significant comorbidities that included obesity, hypertension, autoimmune disease and/or congenital heart disease. Two of the maternal deaths occurred during the early postpartum period and one in the first trimester. One patient died from respiratory failure before she could have benefitted from COVID-19 therapeutics. One died from a postpartum pulmonary embolus after recovering from a prolonged COVID-19

hospitalization where she received venous thromboprophylaxis during and after her hospital stay. A third patient died of respiratory failure after a prolonged ICU stay despite multiple COVID-19 therapeutics. One of the two neonates born to women, who died postpartum, was healthy. The other neonate was preterm and admitted to the NICU for respiratory distress; SARS-CoV-2 testing data was missing for this neonate.

Maternal and Pregnancy Outcomes by Trimester of Infection and Severity of SARS-CoV-2 Infection

Final pregnancy outcome data were available for 65.8% (158/240) of pregnant patients with a SARS-CoV-2 infection, including 7.9% (3/38) patients with infection the first trimester, 40.3% (27/67) in the second trimester, and 94.8% (128/136) in the third trimester (Table 2). For the three patients with pregnancy outcome data associated with a SARS-CoV-2 infection in the first trimester, there was one maternal death and two spontaneous abortions. For the remaining 155 patients with infections in the second and third trimester, nearly all patients had a live birth (98.7%, n=153; Table 5). There were two stillbirths in this study; neither stillbirth was attributed to SARS-CoV-2 infection. An extensive investigation to determine the cause of death was performed in one case, as previously reported, and a genetic cause was attributed to the second death.(2) Maternal and delivery characteristics were similar between women with SARS-CoV-2 infections in the second and third trimester (Table 5).

At the time of delivery for pregnant patients with second and third trimester SARS-CoV-2 infections, 43.2% (67/155) were considered recovered from COVID-19 (including 11 women experiencing severe disease earlier in pregnancy); an additional 49.7% (77/155) had mild COVID-19, and 7.1% (11/155) had severe/critical COVID-19 at delivery (Table 6). Pregnant women with severe/critical COVID-19 at delivery were more likely to have a preterm birth (45.4% severe/critical COVID-19 vs. 5.2% mild COVID-19 vs. 9.0% recovered, $p<0.001$) and to be delivered due to COVID-19 (63.6% severe/critical COVID-19 vs. 2.6% mild COVID-19 vs. 0% recovered, $p<0.001$). The frequency of gestational diabetes and new onset hypertensive disorders of pregnancy or postpartum, were similar by COVID-19 status at delivery (Table 6).

Neonatal Outcomes

There were three sets of twins for a total of 156 live-born neonates. Neonates born to mothers with severe or critical COVID-19 at the time of delivery were more likely to be low birthweight (<2500 g) and more likely to be admitted to the NICU for fetal indications than those born to women with mild COVID-19 or recovered from COVID-19 at the time of delivery (Table 6). Of the 144 neonates with SARS-CoV-2 test results available, one-third were tested at least once (31.3%, 45/144) and none tested positive (Table 5). The remaining two-thirds were not tested for SARS-CoV-2. Neonatal testing was most common among pregnant patients with severe COVID-19 at delivery (77.9%, 7/9), but conducted in only half of patients with mild COVID-19 at delivery (44.9%, 35/77); SARS-CoV-2 testing was uncommon among women considered COVID-19 recovered at delivery (5.3%, 3/57). Neonates were generally healthy with the most common diagnoses of respiratory distress (n=6), hyperbilirubinemia (n=4) and possible sepsis (n=3). Other diagnoses included meconium aspiration syndrome, metabolic acidosis, hypoglycemia, supraventricular tachycardia, pneumothorax and hypotonia.

Discussion

Principal Findings

While most pregnant patients with SARS-CoV-2 in pregnancy experienced mild disease and recovered, 1 in 11 developed severe or critical disease, 1 in 10 were hospitalized specifically for a COVID-19 concern, 1 in 30 were admitted to the ICU for respiratory concerns, 1 in 60 were mechanically-ventilated, and 1 in 80 died. Case fatality rates in pregnant patients with SARS-CoV-2 infections were nearly 14-fold higher than that of similarly-aged individuals in Washington State with COVID-19, making up nearly 10% of SARS-CoV-2 deaths among 20-39 year olds in Washington State. In addition, the case fatality rate in pregnant and recently pregnant patients with SARS-CoV-2 infections of 1,250/100,000 pregnancies is in stark contrast to the Washington State maternal mortality rate of 37.3/100,000 live births and pregnancy-related maternal mortality rate

of 11.2/100,000 live births.(21) Nearly half of the hospitalized patients delivered during a hospital admission for respiratory concerns, which raises the risk for preterm birth and associated complications of prematurity.(22) Notably, these deaths occurred after the 'first wave' in Washington State and at a time when remdesevir and other therapeutics (dexamethasone) were administered to many patients in our study. The case-fatality rate and morbidity associated with SARS-CoV-2 infections in pregnancy in Washington States provides additional evidence for enhanced COVID-19 disease in pregnancy.

Results in the Context of What is Known

The CDC listed pregnant patients as a population at increased risk for severe COVID-19 disease only recently after an expanded analysis of U.S. surveillance data of reproductive aged women with SARS-CoV-2 infections.(9, 12, 23) Pregnant patients with SARS-CoV-2 were at increased risk of ICU admission, ventilation, and death; yet pregnancy status was missing for 64.5% of COVID-19 cases.(12) Notably, in mid-October of 2020, the CDC reported only 45 maternal deaths in pregnant women with confirmed SARS-CoV-2 infections across the U.S.(9); if complete, this would mean that the three cases in our study population represented 7% of the total maternal deaths in pregnant women with SARS-CoV-2 across the U.S. despite annual births among our study sites making up an estimated 1.4% of the total nationwide.(24) This is most likely due to underreporting and not a higher death rate in Washington State. There is a long history of underreporting pregnancy status in important surveillance data including infectious disease reporting and in US death records (25), while efforts are ongoing to rectify this we are concerned that pregnant patients are at increased risk for maternal mortality due to COVID-19 and that deaths in this unique group may be significantly undercounted in the U.S.

Our finding that deaths in pregnant patients contributed disproportionately to deaths from COVID-19 among 20-39 years old in Washington State is similar to what was observed during the influenza A virus H1N1 2009 pandemic. While approximately 1% of the U.S. population is pregnant at any point in time, deaths in pregnant women contributed 5.7% of all deaths from influenza A virus H1N1 2009 in pooled data from a

systematic review.(26) Similar to deaths in pregnant patients from Influenza A virus (IAV) H1N1 2009, all three pregnant patients with a SARS-CoV-2 infection in our study who died were obese or had other underlying conditions.(14, 27, 28) Notably, two of three maternal deaths occurred postpartum after a prolonged or second hospitalization for COVID-19-associated complications highlighting the postpartum period as a high-risk period; this was also a high-risk time period for maternal mortality due to IAV H1N1 2009.(29) However, unlike the IAV H1N1 2009 pandemic when pregnant women were quickly identified in the U.S. as a high-risk and vulnerable group(30, 31), pregnancy was not identified as a high-risk condition for COVID-19 disease or mortality for the first, critical eight months of the pandemic. Given the similarity in clinical course between COVID-19 and IAV H1N1 2009 with an increased risk for mortality during pregnancy and the postpartum period, we strongly recommend that pregnant patients should be considered a high-risk population to novel highly pathogenic respiratory viruses until proven otherwise by population-based studies with good ascertainment of pregnancy status.

Research Implications

The impact of COVID-19 on maternal and neonatal health is limited by the paucity of data sets that capture outcomes from hospitalized and non-hospitalized cases across all trimesters of pregnancy. In our study in Washington State, pregnant patients with severe or critical disease at the time of delivery had a higher likelihood of preterm birth, which can have important long-term adverse impacts on the lifelong health of the child (e.g. brain, lung injury).(32, 33) When comparing outcomes by trimester of SARS-CoV-2 infection, pregnancy complications and delivery outcomes were similar; however, the number of delivery outcomes for second trimester infections were small so this finding does not prove an absence of differential outcomes by trimester of infection. Further studies of pregnancy outcomes by trimester of infection will be important to determine if there is an impact of pregnancy complications, fetal growth and neonatal outcomes. Finally, it will be important to follow neonates for many years to determine the long-term sequelae of the spectrum of maternal COVID-19 disease; in particular, the risk of

neuropsychiatric disease, such as autism spectrum disorder, is important to determine following a several maternal infection.(34, 35)

Strengths and Limitations

This study's major strength was its capture of confirmed SARS-CoV-2 cases from 35 sites across Washington State representing 61% of annual deliveries across the state. Including cases from all trimesters of pregnancy and regardless of symptoms status enabled a more thorough examination of spectrum of SARS-CoV-2 infection in pregnancy. In addition, we ascertained the reason for hospitalization, distinguished between hospitalizations that were for COVID-19 disease, delivery or another indication, and assessed outcomes by whether the pregnant patient had active COVID-19 at the time of delivery versus earlier in pregnancy. This study also had limitations, including the potential for under-ascertainment of asymptomatic and milder cases, particularly earlier in pregnancy, despite several methods for case detection across sites. As a result the severity of cases and our hospitalization and maternal mortality estimates may be an under- or overestimate of the statewide rates. Moreover, data collection was completed before pregnancy outcome data for first trimester and most second trimester pregnancies would have occurred limiting the inference we are able to make about trimester of infection and adverse maternal and neonatal outcomes. Lastly, the SARS-CoV-2 case fatality point estimates in pregnant patients and the relative comparisons to crude COVID-19 case fatality rates among similarly aged Washingtonians should be cautiously interpreted given the rare outcomes under study, potential for selection bias, and use of imperfect denominators for comparison due to limitations in publicly-available data (e.g., all 20-39 year olds – females and males in Washington State). The ideal state-wide comparison group would have been non-pregnant reproductive-aged women with SARS-CoV-2 infections which is not currently publicly-available. Nevertheless, this study provides further evidence that pregnant patients with COVID-

19 are at an elevated risk for poor maternal outcomes and should be targeted for pregnancy and infant outcome surveillance.

Conclusions

Our finding of a markedly higher mortality rate among pregnant people with SARS-CoV-2 infection in a statewide multi-center cohort study representing the majority of annual births in Washington state is compelling evidence that pregnant patients are a population at high-risk for morbidity and mortality associated with SARS-CoV-2 infection.(9) The overall 1 in 80 maternal mortality rate in pregnancy coupled with the potential overrepresentation of pregnant people in Washington State's SARS-CoV-2 deaths in 20-39 year olds is cause for concern. Further, these maternal deaths represented 7% of those known to the CDC in mid-October despite our population representing only 1.4% of the nation's births; this suggests undercounting of maternal deaths, which is likely given the missing pregnancy status in 65% of COVID-19 case reports.(12) We also found a significantly higher likelihood of preterm birth in pregnant patients with severe/critical COVID-19 disease is concerning given the long-term adverse outcomes on a child's health through the life course.(10, 11, 36) Greater attention to pregnant patients as a unique population at higher risk of SARS-CoV-2 infection sequelae, is critical to preventing maternal and neonatal morbidity and mortality. This data strongly supports the need to offer vaccination to pregnant women at risk for acquiring SARS-CoV-2 infection and include pregnant people in clinical trials and other observational evaluations of vaccines and COVID-19 therapies.(37-42)

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Table 1. Demographics and Comorbidities by Hospitalization Status in Pregnant Patients with SARS-CoV-2 Infection

Characteristics	All Pregnant Patients (N=240)[i]	Not Hospitalized for COVID-19 concern (N=216)	Hospitalized for COVID-19 concern (N=24)	p-value
Demographics				
Age	28 (24, 34)	28 (24,33)	32 (26, 35)	0.04
Race				0.14
American Indian/Alaska Native	10 (4.2)	8 (3.7)	2 (8.3)	
Asian	8 (3.3)	8 (3.7)	0 (0)	
Native Hawaiian or Other Pacific Islander	8 (3.3)	5 (2.3)	3 (12.5)	
Black or African American	20 (8.3)	19 (8.8)	1 (4.2)	
White	113 (47.1)	104 (48.2)	9 (37.5)	
Multiracial	2 (0.8)	2 (0.9)	0 (0)	
Other	28 (11.7)	26 (12.0)	2 (8.3)	
Unknown	51 (21.3)	44 (20.4)	7 (29.2)	
Ethnicity				0.29
Hispanic or Latino	126 (52.5)	117 (54.2)	9 (37.5)	
Not Hispanic or Latino	108 (45.0)	94 (43.5)	14 (58.3)	
Unknown	6 (2.5)	5 (2.3)	1 (4.2)	
Type of Insurance at diagnosis				0.11
Public	160 (66.7)	146 (67.6)	14 (58.3)	
Private	74 (30.8)	66 (30.6)	8 (33.3)	
Other	4 (1.7)	2 (0.9)	2 (8.3)	
Uninsured	1 (0.4)	1 (0.5)	0 (0)	

Unknown	1	(0.4)	1	(0.5)	0	(0)	
Pregnancy History[ii]							
Parity	1	(1-3)	1	(1-2)	1.5	(1-4)	0.08
History of preterm birth	23	(9.6)	21	(9.8)	2	(8.3)	0.82
Pre-pregnancy comorbidities or underlying conditions							
Any comorbidity or underlying condition (excluding obesity)[iii]	49	(20.4)	38	(17.6)	11	(45.8)	0.001
Asthma	20	(8.3)	15	(6.9)	5	(20.8)	0.02
Type 2 diabetes	13	(5.4)	10	(4.6)	3	(12.5)	0.11
Hypertension	11	(4.6)	6	(2.8)	5	(20.8)	<0.001
Cardiovascular disease	6	(2.5)	5	(2.3)	1	(4.2)	0.58
Autoimmune disease	4	(1.7)	2	(0.9)	2	(8.3)	<0.01
Hypothyroidism	4	(1.7)	3	(1.4)	1	(4.2)	0.31
Pre-pregnancy BMI[iv]							0.02
Underweight (<18.5)	3	(1.3)	3	(1.5)	0	(0)	
Normal (18.5-24.9)	57	(25.3)	55	(26.7)	2	(10.5)	
Overweight (25.0-29.9)	63	(28.0)	56	(27.2)	7	(36.8)	
Obese (≥30.0)	102	(45.3)	92	(44.7)	10	(52.6)	
Class 3 Obesity (BMI ≥40)[iv]	17	(7.6)	13	(6.3)	4	(21.1)	0.02

[i] Summarized as n(%) or median(IQR).

[ii] Parity and history of preterm birth missing for 1 participant.

[iii] Comorbidities assessed for in data collection tool included: diabetes, asthma, reactive airway disease, hypertension, hypothyroidism, cardiovascular disease, auto-immune disease, HIV, immunosuppressive medication use, cirrhosis, Hepatitis A history, Hepatitis C antibody, prior or current cancer, tuberculosis, pre-pregnancy kidney disease, COPD, seizure disorder, cerebrovascular disease.

[iv] Data only available for 225 patients. Pre-pregnancy weight or weight prior to 12 weeks gestational age was used if pre-pregnancy weight not available. For one patient, their 14 weeks of gestation weight was used to calculate pre-pregnancy BMI.

Table 2. COVID-19 Disease Severity, Hospitalization and Outcomes by Trimester of Infection in Pregnant Patients

Characteristic	All Pregnant Patients	Hospitalization Status			Trimester of SARS-CoV-2 Infection			
	N=240[i]	Not Hospitalized for COVID-19 concern (N=216)	Hospitalized for COVID-19 concern (N=24)[ii]	p-value	First (N=38)	Second (N=67)	Third (N=135)	p-value
Trimester of Infection[iii]				<0.001				
First	38 (15.8)	37 (17.1)	1 (4.2)					
Second	67 (27.9)	62 (28.7)	5 (20.8)					
Third	135 (56.3)	117 (54.2)	18 (75.0)					
Symptomatic at first COVID-19 positive test[iii]				0.02				<0.001
Asymptomatic	55 (22.9)	54 (25.0)	1[iv] (4.2)		3 (7.9)	3 (4.5)	49 (36.3)	
Symptomatic	185 (77.1)	162 (75.0)	23 (95.8)		35 (92.1)	64 (95.5)	86 (63.7)	
Disease Severity				<0.001				0.28
Mild	218 (90.8)	213 (98.6)	5 (20.8)		37 (97.4)	62 (92.5)	119 (88.2)	
Severe	18 (7.5)	3[v] (1.4)	15 (62.5)		0 (0)	4 (6.0)	14 (10.4)	
Critical	4 (1.7)	0 (0)	4 (16.7)		1 (2.6)	1 (1.5)	2 (1.5)	
Outcomes								
Hospitalized for COVID-19 Concern	24 (10.0)				1 (2.6)	5 (7.5)	18 (13.3)	0.11
Admitted to ICU	8 (3.3)	0 (0.0)	8 (33.3)		0 (0)	1 (1.5)	7 (5.2)	0.74
Maternal Death	3 (1.3)	0 (0.0)	3 (12.5)	<0.001	1 (2.6)	1 (1.5)	1 (0.7)	0.64
Final pregnancy outcome[vi]	158 (65.8)	135 (62.5)	23 (95.8)	0.001	3 (7.9)	27 (40.3)	128 (94.8)	<0.001
COVID-19 at final outcome[vii]	90 (57.0)	78 (57.8)	12 (52.1)	0.62	2 (66.7)	2 (7.4)	86 (67.2)	<0.001
Recovered from COVID-19 at final outcome	68 (43.0)	57 (42.2)	11 (47.8)		1 (33.3)	25 (92.6)	42 (32.8)	

Gray shading indicates cells with no data.

[i] Summarized as n(%) or median(IQR).
[ii] One patient was hospitalized and admitted to ICU twice several months apart..
[iii] At time of first positive SARS-CoV-2 test
[iv] This patient was tested due to a known exposure to COVID-19 and became symptomatic prior to hospitalization.
[v] All three patients had dyspnea but were not ultimately hospitalized.
[vi] Includes one maternal death and two spontaneous abortions in pregnant patients with first trimester SARS-CoV-2 infections.
[vii] Includes pregnant patients with mild or severe/critical COVID-19 at the time of final pregnancy outcome

Table 3. Disease severity and COVID-19 therapies used in 24 pregnant patients hospitalized for COVID-19 concern

Characteristic	Hospitalized due to COVID-19 concern (N=24)[i]	
	N	**n (%) or median (IQR)**
Gestational age at admission[ii]	23	32.4 (26-36.1)
Admitted for COVID-19 concern & delivery indication	24	3 (12.5)
Delivered while admitted for COVID-19 concern[iii]	22	9 (40.9)
Admitted to ICU	24	8 (33.3)
Highest level of oxygen support	24	
None		5 (20.8)
Nasal Cannula		8 (33.3)
High Flow Nasal Cannula		3 (12.5)
Non-Rebreather Mask		4 (16.7)
Mechanical Ventilation		4 (16.7)
COVID-19 therapies[iv]	24	
None		7 (29.1)
Remdesivir		9 (37.5)
Hydroxychloroquine		2 (8.3)
Convalescent Plasma		2 (8.3)
Dexamethasone		3 (12.5)
Vasopressor support	24	4 (16.7)
Laboratory Measures[v]		**n (%) or median (range)**
Lowest white blood cell count (10^3 per µL blood)	23	6.1 (2.8-19)
Lymphopenia (≤5.6 x 10^3 per µL blood)	23	10 (43.5)
Highest aspartate aminotransferase (AST, units/L)	22	46 (12-377)
Elevated AST (≥33 unitsl/L)	22	17 (77.3)

Highest D-Dimer (µg/mL)	17	1.5	(0.2-4.5)
Elevated D-Dimer (>3.3 µg/L)	17	5	(29.4)
Highest C-Reactive Protein (mg/L)	15	25.7	(1.6-281.1)
Elevated C-Reactive Protein (≥22.3 mg/L)	15	8	(53.3)
Highest creatinine (mg/dL)	23	0.7	(0.4, 1.2)
Elevated creatinine (>0.9 mg/dL)	23	1	(4.4)

[i] N (%) or median (IQR). One patient was hospitalized twice several months apart; clinical details are reported for the first hospitalization only during acute COVID-19 infection. An additional patient diagnosed with SARS-CoV-2 at delivery was subsequently re-admitted for COVID-19 concern postpartum.
[ii] N=23, excluding one patient who was admitted postpartum.
[iii] N=22, excluding one patient who was admitted postpartum and one first trimester maternal death
[iv] Patients receiving multiple targeted COVID-19 therapies are included in each relevant category.
[v] Laboratory values represented the highest/lowest detected during hospitalization; for some patients this was postpartum. Thresholds for abnormal laboratory values were specific to pregnancy.[21]

Table 4. SARS-CoV-2 Hospitalizations and Case-Fatality Rates Among Pregnant Women in Washington State: Comparisons with Washington State Data COVID-19 Surveillance Data

Population	n	N	Rate		Rate Ratio		Rate Difference	
COVID-19 Hospitalization								
			%	**(95%CI)**	**RR**	**(95%CI)**	**RD %**	**(95%CI)**
WA-CPC: Pregnant patients with SARS-CoV-2	24	240	10.0	(6.4-14.9)	-		-	
WA State: 20-39 year olds with SARS-CoV-2	985	34902	2.8	(2.6-3.0)	3.5	(2.3-5.3)	7.2	(3.2, 11.2)
COVID-19 Deaths								
			Deaths/ 100,000	**(95%CI)**	**RR**	**(95%CI)**	**Deaths/ 100,000**	**(95%CI)**
WA-CPC: Pregnant patients with SARS-CoV-2	3	240	1250.0	(257.8-3653.0)	-		-	
WA State: 20-39 year olds with SARS-CoV-2	32	34902	91.7	(62.7, 129.4)	13.6	(2.7-43.6)	1158.3	(-256.5, 2573.2)

Publicly available COVID-19 hospitalization and mortality data for 20-39 year olds in WA State were obtained from the WA-DOH COVID-19 surveillance dashboard.(19) The rate ratio compares the SARS-COV-2 infection hospitalization and mortality rates in pregnant patients in Washington State compared to the 20-39 year old general population. The rate difference indicates the absolute rate difference associated with SARS-CoV-2 infections in pregnant patients in Washington State compared to the 20-39 year old adults.

Table 5. Maternal, delivery, and neonatal outcomes among pregnant patients with SARS-CoV-2 infections overall and by trimester of infection

Characteristics[i]	Overall[ii]	Trimester of Infection		
		Second	Third	p-value
Pregnancy Outcome	**N=155**	**N=27**	**N=128**	
Livebirth	153 (98.7)	26 (96.3)	127 (99.2)	
Stillbirth	2 (1.3)	1 (3.7)	1 (0.8)	
Delivery Characteristics	**N=155**	**N=27**	**N=128**	
Timing				
Time from first COVID-19 positive test to outcome (days)	20 (2-58)	99 (85-105)	8 (1-35)	0.0001
Gestational age at delivery (weeks)	39.1 (38.1-40)	38.4 (37.6-39.1)	39.1 (38.4-40)	0.02
Preterm birth	15 (9.7)	4 (14.8)	11 (8.6)	0.32
Due to preterm labor or PPROM	7 (46.7)	3 (75.0)	4 (36.4)	0.19
Mode of Delivery				
Induction (N=121 with any labor)	49 (40.5)	9 (39.1)	40 (40.8)	0.88
Cesarean delivery	55 (35.5)	9 (33.3)	46 (35.9)	0.80
Delivery induced or performed due to COVID-19[iii]	9 (5.8)	0 (0)	9 (7.0)	0.16
Obstetrical and Fetal Complications	**N=155**	**N=27**	**N=128**	
Gestational diabetes	16 (10.3)	2 (7.4)	14 (10.9)	0.58
New onset hypertensive disorder of pregnancy or postpartum[iv]	19 (12.3)	3 (11.1)	16 (12.3)	0.84
Diagnosed at or after COVID-19 diagnosis	17 (89.5)	3 (100)	14 (87.5)	0.52
Non-reassuring fetal status / fetal distress	19 (12.3)	3 (11.1)	16 (12.5)	0.84
Neonatal Outcomes	**N=156[v]**	**N=26**	**N=130**	
Birthweight (g)[vi]	3249 (2905, 3640)	3206 (2887, 3510)	3249 (2906, 3663)	0.42
Low birthweight (<2,500 g)	8 (5.1)	0 (0)	8 (6.2)	0.19
SARS-CoV-2 testing performed[vii]	45 (31.3)	1 (4.2)	44 (36.7)	0.002
SARS-CoV-2 positive	0 (0)	-	-	
NICU admission[viii]	11 (7.1)	1 (3.9)	10 (7.8)	0.48

Abbreviations: g, grams; HELLP, hemolysis, elevated liver enzymes, and a low platelet count; NICU, neonatal intensive care unit; PPROM, preterm premature rupture of membranes.

[i] Presented as n(%) and median(IQR).
[ii] Excludes three cases of SARS-CoV-2 infection during the first trimester. Two cases ended in spontaneous abortion and one led to a maternal death.
[iii] COVID-19 was either the singular indication or a contributory indication for delivery.
[iv] A new onset hypertensive disorder of pregnancy or postpartum included any of the following diagnoses: new onset gestational hypertension, preeclampsia, eclampsia, chronic hypertension with superimposed preeclampsia, and HELLP.
[v] Live births only (N=156). There were 3 twin gestations.
[vi] Birthweight is missing for 1 neonate (N=155).
[vii] Testing data missing for 12 neonates, for a total of 24 neonates born to pregnant patients with second trimester SARS-COV-2 infections and 120 neonates born to pregnant patients with third trimester SARS-COV-2 infections.
[viii] NICU admission occurred for a neonatal health indication. Does not include NICU admission solely for COVID-19 precautions. N=155, data missing for one neonate.

Table 6. Maternal, delivery, and neonatal outcomes among pregnant patients with SARS-CoV-2 infections by infection status at delivery

Characteristics[i]	COVID-19 Status at Delivery			
	Recovered at delivery	Mild COVID-19 at delivery	Severe/Critical COVID-19 at delivery[ii]	p-value
Delivery Characteristics[iii]	**N=67**	**N=77**	**N=11**	
Timing				
Time from first COVID-19 positive test to outcome (days)	58 (34092)	3 (0-11)	8 (3-14)	0.0001
Gestational age at delivery (weeks)	39 (37.7-40)	39.3 (38.6-40.1)	37 (33.9-39.1)	<0.01
Preterm birth	6 (9.0)	4 (5.2)	5 (45.4)	<0.001
Due to preterm labor or PPROM	5 (83.3)	1 (25.0)	1 (20.0)	0.07
Mode of delivery				
Induction (N=121 with any labor)	23 (39.7)	24 (41.4)	2 (40.0)	0.98
Cesarean delivery	22 (32.8)	26 (33.8)	7 (63.6)	0.13
Delivery induced or performed due to COVID-19[iv]	0 (0)	2 (2.6)	7 (63.6)	<0.001
Obstetrical or Fetal Complications	**N=67**	**N=77**	**N=11**	
Gestational diabetes	8 (11.9)	6 (7.8)	2 (18.2)	0.48
New onset hypertensive disorder of pregnancy or postpartum[v]	5 (7.5)	14 (18.2)	0 (0)	0.07
Diagnosed at or after COVID-19 diagnosis	5 (100.0)	12 (85.7)	0 (0)	0.37
Non-reassuring fetal status / fetal distress	4 (6.0)	9 (11.7)	6 (54.6)	<0.001
Neonatal Outcomes[vi]	**N=67**	**N=78**	**N=11**	
Birthweight (g)[vii]	3261 (2950, 3560)	3298 (2950, 3705)	2690 (2490, 3020)	<0.01
Low birthweight (<2,500 g)	2 (3.0)	3 (3.9)	3 (27.3)	0.003
SARS-CoV-2 testing performed[viii]	3 (5.3)	35 (44.9)	7 (77.9)	<0.001
NICU admission[ix]	2 (3.0)	6 (7.7)	3 (27.3)	0.01

Abbreviations: HELLP, hemolysis, elevated liver enzymes, and a low platelet count; NICU, neonatal intensive care unit; PPROM, preterm premature rupture of membranes.

[i] Presented as n(%) and median(IQR).
[ii] One patient was re-admitted several months after a severe COVID infection due to a COVID-associated complication and was considered to have "Active COVID-19" in this analysis although she had negative polymerase chain reaction testing at the time.
[iii] N=155, excluding two spontaneous abortions.
[iv] COVID-19 was the singular indication or a contributing indication for delivery.
[v] Data collection tools included new onset gestational hypertension, preeclampsia, eclampsia, chronic hypertension with superimposed preeclampsia, and HELLP.
[vi] Live births only (N=156). There were 3 twin gestations.
[vii] Birthweight is missing for 1 neonate (N=155).
[viii] Testing data missing for 12 neonates, for a total of 57 neonates born to pregnant patients considered COVID-19 recovered at delivery, 78 neonates born to pregnant patients with mild COVID-19 at delivery, and 9 neonates born to pregnant patients with severe COVID-19 at delivery.
[ix] NICU admission occurred for a neonatal health indication. Does not include NICU admission solely for COVID-19 precautions. N=155, data missing for one neonate.